so as to be consistent with the general statements in the specification as well as the specific examples, as more fully discussed below.

The change on page 5, line 18 of the specification from a ratio of 12: 1 to 40:1 is supported by the disclosure on page 4, lines 25-30, of the specification, wherein it is stated that a daily dosage of about 30 to 600 mg. of the compound of formula I and about 15 to 300 mg. of the diuretic may be used. Therefore, as little as 15 mg. of diuretic can be used with as much as 600 mg. of the compound of formula I, a ratio of 40:1.

The change in Claim 13 of the lower limit of the amounts of both the compound of the formula and the diuretic is to reflect the fact that more than one dose of composition can be administered per day. Thus, as stated on page 5, lines 4-9, of the specification, if the combination is administered four times daily, as little as 5 mg. of the compound of formula and 2.5 mg. of the diuretic may be administered at any one time.

With the inclusion of the limitations of Claim 2 into Claim 1, it is submitted that the rejection of Claim 1 and dependent Claims 4 through 8 under the provisions of 35 USC 112, paragraph 2, is manifestly obviated.

Reconsideration of the rejection of all of the claims under the provisions of 35 USC 103 over the Ondetti et al. reference (R) in view of the Johnson et al. reference (S) is respectfully requested. Ondetti et al, discloses certain compounds within the scope of the formula in Claims 1 and 13 and their use as antihypertensive agents. The reference fails to disclose, however, any combination of these compounds and a diuretic.

The Johnson et al. reference discloses the nonapeptide, SQ20,881, as a hypotensive agent, and its use in combination with the diuretic, frusemide (furosemide), which is one of the diuretics applicants employ in their combination. The nonapeptide is administered intravenously. It is not clear how the furosemide is administered.

Based on the combination of these references and the discussion in the Ondetti et al. reference that the mode of action of SQ20,881 and the compounds of the formula in the instant claims is similar, it is the Examiner's position that it would be obvious to substitute the compounds of the formula in the instant claims for the SQ20,881 in the Johnson et al. reference.

It is respectfully submitted that the proposed combination of references is improper and in any event fails to anticipate or suggest applicants' claimed invention for the following reasons:

1. Structurally SQ20,881 and the instant compounds are too dissimilar in structure for one to suggest the other. SQ20,881 is a nonapeptide containing nine aminoacids. Applicants' compounds, on the other hand, are acylated prolines, containing only one aminoacid. The fact that the reference compound and the instant compounds are believed to function as antihypertensive drugs through the same mechanism of activity is not believed to be sufficient basis to suggest the substitution of one for the other.

2. SQ20,881 is active only parenterally and cannot be used orally as a viable antihypertensive drug. In contrast, the instant claims are limited to method of treatment and compositions to be administered orally. Certainly the

teaching of the parenteral use of a compound, devoid of meaningful oral activity, would not suggest the substitution of any compound therefor for oral administration.

3. From the point of view of the results obtained, the Johnson et al. reference merely states that the frusemide enhanced the other substance. The quantitative data on page 14 in this application show that the combination of (D-3-mercapto-2-methylpropanoyl)-L-proline with furosemide results in a marked reduction of blood pressure, 27%, not merely an enhancement or additive effect. In the data on pages 14-17, it is shown that in long term treatment with hydrochlorothiazide alone no significant decrease in blood pressure is demonstrated. A combination of hydrochlorothiazide and the compound named above achieves a 30% reduction in blood pressure, more than a mere additive effect, and also only the combination shows a 100% survivor rate. These data also show the differences obtained by the diuretics alone, yet the marked effectiveness of the combination.

It is noted that in the case of Claims 11, 21, 23 and 25, the diuretics named do not occur in the references. Moreover, nowhere in the references is there disclosed a combination product, as called for in Claims 13 through 25.

It is respectfully submitted that the combination of references applied against the claims is not suggested because of the differences inherent in the disclosures with respect to the types of compounds and the routes of administration as discussed above. Moreover, the results obtained

by the claimed subject matter, as shown in the specification, could not be foretold from the prior art disclosures.

It is therefore submitted that the claims, as now amended, define patentable subject matter.

Respectfully submitted,

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